CLINICAL REVIEWS

# Benefits and Risks of Third-Generation Oral Contraceptives

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***OBJECTIVE:*** **To evaluate the risks and benefits of third-generation oral contraceptives.**

***DATA SOURCES:*** **A MEDLINE search was done for English language articles published from 1985 through 1998 relating to the side-effect profile of third-generation oral contraceptives or their association with cardiovascular or thromboembolic disease. All articles containing original data were included.**

***DATA SYNTHESIS:*** **The risk of venous thromboembolism appears to be 1.5- to 2.7-fold greater in users of third-generation, compared with second-generation, oral contraceptives. Compared with nonusers, women who use third-generation oral contraceptives may have a 4.8- to 9.4-fold greater risk of venous thromboembolism. Users of third-generation oral contraceptives do not appear to have an increased risk of myocardial infarction compared with nonusers and may have risk of myocardial infarction of 0.26 to 0.7 compared with second-generation users. Whether third-generation oral contraceptives are associated with a decreased stroke risk is still not clear.**

***CONCLUSIONS:*** **Although third-generation oral contraceptives most likely increase a user's risk of venous thromboembolism, their improved side-effect profile and their possible decreased association with myocardial infarction and stroke may make them a useful new class of oral contraceptives for most women except those at increased risk of venous thrombosis.**

***KEY WORDS:*** **contraceptives, oral; desogestrel; thromboembolism; myocardial infarction; cerebrovascular disorders.**
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When used consistently, oral contraceptives are a highly effective means of birth control. However, some women discontinue their use because of bothersome side effects such as acne, hirsutism, and weight gain. Oral contraceptives adversely affect thrombolysis, carbohydrate metabolism, and lipid profiles, and this may be why they have been associated with an increased risk of myocardial infarction and stroke in case-control and cohort studies.[1–4] Because these minor and major side effects have been correlated with the androgenicity of the progestin, third-generation oral contraceptives were created to decrease the amount of androgenic activity. They contain only low doses of estrogen (≤35 μg of ethinyl estradiol) combined with either desogestrel, norgestimate, or gestodene (gestodene is not FDA-approved for use in the United States), which are progestins with low androgenic activity (Table 1). Although they appear to be as effective as previous oral contraceptives and have a decreased incidence of side effects, they have been associated with an increased rate of venous thromboembolism. This prompted some regulatory agencies and professional groups to recommend restricting the prescribing of third-generation oral contraceptives, but others contend that the data are not convincing enough to limit their use. This article will review the risks and benefits of third-generation oral contraceptives.

## METHODS

A MEDLINE search of articles published from 1985 to 1998 was performed. The terms *oral contraceptives*, *desogestrel*, *third-generation oral contraceptives*, *gestodene*, and *norgestimate* were combined with the terms *thromboembolism*, *myocardial infarction*, *cerebrovascular disorders*, *adverse effects*, and *stroke*. English language articles containing original data on the association between third-generation oral contraceptives and thromboembolism or cardiovascular disease were reviewed by both authors. Studies on the side effects of third-generation oral contraceptives and editorials on the controversy surrounding the relation between third-generation oral contraceptives and venous thrombosis, myocardial infarction, and stroke were also evaluated. In addition, references of articles were reviewed for other studies not identified by the MEDLINE search. All published studies containing original data on the relation between third-generation oral contraceptives and thromboembolic disease, myocardial infarction, or stroke are included in this review.

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**Table 1. Third-Generation and Second-Generation Oral Contraceptives Available in the United States***

| Name | Generation | Type of Formulation | Estrogen (μg) | Progestin (mg) |
|---|---|---|---|---|
| Desogen | Third | Monophasic | Ethinyl estradiol (30) | Desogestrel (0.15) |
| Ortho-Cept | Third | Monophasic | Ethinyl estradiol (30) | Desogestrel (0.15) |
| Ortho-Cyclen | Third | Monophasic | Ethinyl estradiol (35) | Norgestimate† (0.25) |
| Ortho-Tri-Cyclen | Third | Triphasic | Ethinyl estradiol (35) | Norgestimate† (0.180, 0.215, 0.250) |
| Levlen | Second | Monophasic | Ethinyl estradiol (30) | Levonorgestrel (0.15) |
| Nordette | Second | Monophasic | Ethinyl estradiol (30) | Levonorgestrel (0.15) |
| Tri-Levlen | Second | Triphasic | Ethinyl estradiol (30, 40, 30) | Levonorgestrel (0.05, 0.075, 0.125) |
| Triphasil | Second | Triphasic | Ethinyl estradiol (30, 40, 30) | Levonorgestrel (0.05, 0.075, 0.125) |

**Only the second-generation oral contraceptives containing levonorgestrel are listed as this was the predominant second-generation progestin used in the studies on venous thromboembolism, myocardial infarction, and stroke.*

†*Although norgestimate is sometimes classified as a second-generation oral contraceptive because its main metabolite is levonorgestrel, most sources consider it a third-generation oral contraceptive as it has a lower androgenic activity.*

## MINOR SIDE EFFECTS

Some of the most bothersome side effects of oral contraceptives, such as acne, hirsutism, and weight gain, are associated with androgens. Because they contain progestins with low androgenic activity, third-generation oral contraceptives should be associated with a decreased incidence of these problems. Indeed, in two large noncomparative studies and a randomized clinical trial, users of third-generation oral contraceptives had 25% to 80% improvement in preexisting acne,[5–7] which was more than with the second-generation progestin levonorgestrel.[6] A study of more than 13,000 women found that half had disappearance of their preexisting hirsutism and only 0.4% newly developed it.[7] In comparative and noncomparative studies, third-generation oral contraceptives rarely resulted in significant weight gain,[5,8–11] and compared with second-generation oral contraceptives, were associated with 29% to 45% lower rates of discontinuation due to weight gain.[10]

Breakthrough bleeding or, conversely, amenorrhea are other reasons why women discontinue oral contraceptives. Multicenter studies involving thousands of women found that breakthrough bleeding or spotting occurred in only 3.7% to 12.0% of the cycles,[8,9,12–14] which is similar to the rates in second-generation oral contraceptive users.[8] Amenorrhea occurred in 0% to 1.7% of women using third-generation oral contraceptives.[12–14]

Because of their improved side-effect profile and low rate of bleeding irregularities, third-generation oral contraceptives have generally been associated with lower discontinuation rates than other oral contraceptives, although not significantly so.[15]

## VENOUS THROMBOEMBOLISM

Use of oral contraceptives has long been associated with increased risk of venous thromboembolism. Until recently, this thrombotic risk was attributed solely to the estrogen component of the pill. A series of articles published since 1995 have challenged this theory and have implicated some progestins. Two large case-control studies, the World Health Organization (WHO) Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception involving more than 4,100 women from 21 centers in Africa, Asia, Europe, and Latin America[16,17] and the Transnational Study on Oral Contraceptives and the Health of Young Women involving more than 2,200 women from 10 centers in Germany and the United Kingdom,[18] evaluated venous thrombosis risk by type of oral contraceptive. Both studies found that users of third-generation oral contraceptives had an increased risk of venous thromboembolism when compared with users of levonorgestrel-containing second-generation oral contraceptives (odds ratio [OR] 2.7; 95% confidence interval [CI] 1.6, 4.6;[17] and 1.5 [95% CI 1.1, 2.1],[18] respectively) (Table 2). Bloemenkamp et al., in their 1995 case-control study of 285 women, found that for venous thrombosis in third-generation oral contraceptive users the OR was 8.7 (95% CI 3.9, 19.3), compared with an OR of 3.8 (95% CI 1.7, 8.4) in second-generation users.[19] The two most recent case-control studies by Lidegaard et al.[20] and Bloemenkamp et al.[21] found that users of third-generation oral contraceptives had, respectively, a 1.8-fold and 1.9-fold, increased risk of venous thrombosis compared with second-generation oral contraceptive users. Cohort studies by Jick et al.[22] and Farmer et al.[23] corroborated the case-control studies' findings. When analyzed separately, each of three third-generation progestins, gestodene, desogestrel, and norgestimate, was associated with an increased risk of venous thromboembolism.[17,19–24] (Table 3).

In summary, these studies found that users of third-generation oral contraceptives had a 1.5- to 2.7-fold increased risk of venous thromboembolism when compared with users of levonorgestrel-containing second-generation oral contraceptives or a 4.8- to 9.4-fold increased risk of venous thrombosis compared with nonusers. This would mean that for every 100,000 women who use third-generation oral contraceptives, 17 to 30 would develop a thromboembolic event compared with 8 to 15 users of second-generation oral contraceptives and 3 to 5 nonusers. However, this rate is still much lower than the

**Table 2. Studies of the Relative Risk of Venous Thromboembolism in Users of Third-Generation Compared with Second-Generation Oral Contraceptives***

| Article | Year | Type of Study | Study/ Thrombotic Events, *n* | Adjusted OR (95% CI) for Second-Generation OCP Users† Versus Nonusers | Adjusted OR (95% CI) for Third-Generation OCP Users‡ Versus Nonusers | Adjusted OR (95% CI) for Third-Generation Versus Second-Generation OCP Users |
|---|---|---|---|---|---|---|
| WHO Study Group[16, 17] | 1995 | Case-control | 2,994/769 | 3.4 (2.5, 4.7) | 9.4 (5.6, 15.6) | 2.7 (1.6, 4.6) |
| Transnational Study[18] | 1995 | Case-control | 2,243/471 | 3.2 (2.3, 4.3) | 4.8 (3.4, 6.7) | 1.5 (1.1, 2.1) |
| Bloemenkamp[19] | 1995 | Case-control | 285/126 | 3.8 (1.7, 8.4) | 8.7 (3.9, 19.3) | |
| Lidegaard et al.[20] | 1998 | Case-control | 523/1,597 | 2.08 (1.25, 3.45)§ | 3.73 (2.61, 5.33)§ | 1.79 (1.05, 3.06) |
| Bloemenkamp et al.[21] | 1999 | Case-control | 776/185 | 3.7 (1.4, 9.6) | | 1.9 (0.8, 4.5) |
| Jick et al.[22] | 1995 | Retrospective cohort | 238,130/80 | 2.8 (1.6, 11.0) | 7.5 (3.0, 18.8) | |
| Farmer et al.[23] | 1997 | Retrospective cohort (using age bands)‖ | 540,000/85 | | | 1.68 (1.04, 2.75) |

**OR indicates odds ratio; CI, confidence interval; OCP, oral contraceptive.*

†*The progestin predominantly contained in the second-generation oral contraceptives in these studies is levonorgestrel. In the WHO study, one case and two controls used norgestimate, which is classified as second generation. The Transnational and Lidegaard studies also include norgestimate as a second-generation OCP for its main analysis. However, when Transnational study researchers later recalculate the odds ratio classifying norgestimate as a third-generation OCP, there is no significant change in the odds ratio (OR = 1.6; 95% CI 1.2, 2.2).*[16–19]

‡*The progestins contained in the third-generation OCPs in these studies are predominantly desogestrel or gestodene or both.*

§*The comparison group is former users.*

‖*When Farmer calculated the odds ratio using exact age matching rather than 5-year age bands, the odds ratio was no longer significantly elevated (OR = 1.34; 95% CI 0.74, 2.39).*[23]

60 cases of venous thromboembolism that would be expected per 100,000 pregnancies.[25]

On the basis of these studies, the medicine safety committees of several countries, including the United Kingdom and Germany, strongly cautioned against the use of third-generation oral contraceptives, and faxes were sent to all general physicians advising them to discontinue prescribing third-generation oral contraceptives to their patients. Physicians were inundated with telephone calls from patients. However, the results remain controversial.

One concern is whether the association between third-generation oral contraceptive users and venous thromboembolism could be the result of confounding by age. The WHO, Transnational, and Jick et al. studies used 5-year

**Table 3. Studies of the Relative Risk of Venous Thromboembolism Associated with the Various Third-Generation Progestins***

| Article | Year | Type of Study | Study/ Thrombotic Events, *n* | Adjusted OR (95% CI) for Users of Gestodene Versus Levonorgestrel | Adjusted OR (95% CI) for Users of Desogestrel Versus Levonorgestrel† | Adjusted OR (95% CI) for Users of Norgestimate Versus Levonorgestrel† |
|---|---|---|---|---|---|---|
| WHO Study Group[17] | 1995 | Case-control | 2,994/769 | 3.1 (1.6, 5.9) | 2.4 (1.3, 4.6) | |
| Transnational study[24] | 1996 | Case-control | 2,382/595 | 1.7 (1.1, 2.6)‡ | 1.8 (1.2, 2.6)‡ | 1.9 (1.0, 3.6) |
| Bloemenkamp[19] | 1995 | Case-control | 285/126 | | 2.5 (1.2, 5.2) | |
| Lidegaard et al.[20] | 1998 | Case-control | 523/1,597 | 3.57 (2.37, 5.38)§ | 4.02 (2.43, 6.64)§ | 1.80 (0.43, 7.54)§ |
| Bloemenkamp et al.[21] | 1999 | Case-control | 776/185 | 5.2 (1.3, 20.6)‖ | 4.9 (2.5, 9.4)‖ | |
| Jick et al.[22] | 1995 | Nested case-control | 375/75 | 2.1 (1.1, 4.4)¶ | 2.2 (1.1, 4.4)¶ | |
| Farmer et al.[23] | 1997 | Cohort (using age bands) | 540,000/85 | 1.32 (0.70, 2.49)# | 1.76 (0.91, 3.48)# | |

**OR indicates odds ratio; CI, confidence interval.*

†*Although the predominant second-generation progestin used in these studies is levonorgestrel, 3 women in the WHO study used norgestimate and are classified as second-generation oral contraceptive users.*

‡*When norgestimate is classified as a second-generation progestin, the odds ratios for gestodone versus second-generation oral contraceptives is 1.5 (95% CI 1.0, 2.2) and for desogestrel versus second-generation oral contraceptives is 1.5 (95% CI 1.1, 2.2).*[24]

§*The comparison group is former users.*

‖*The comparison groups is nonusers.*

¶*When the retrospective cohort data from this study are analyzed, the odds ratios for gestodone versus levonorgestrel is 1.8 (95% CI 1.0, 3.2) and for desogestrel versus levonorgestrel is 1.9 (95% CI 1.1, 3.2).*[22]

#*When subjects are matched for exact age instead of 5-year bands, the odds ratio for gestodone versus levonorgestrel is 0.87 (95% CI 0.41, 1.83) and for desogestrel versus levonorgestrel is 0.84, (95 % CI 0.38, 1.85).*[23]

age bands,[16–18,22] which means that the age difference between the case and matched control could be up to 5 years. Because users of third-generation oral contraceptives were significantly younger than second-generation oral contraceptive users and younger users are more likely to develop venous thrombosis,[16,18,22] imprecise matching of age could have created the association between third-generation oral contraceptive users and venous thromboembolism. Indeed, when Farmer et al. performed a nested case-control study and matched subjects by exact age, there was no significant difference in risk of venous thromboembolism between users of third- and second-generation oral contraceptives (OR 1.34; 95% CI 0.74, 2.39)[23]; however, the study by Farmer et al. has been criticized because the diagnosis of venous thromboembolism in the cases was not objectively confirmed, leading to misclassification bias.[26,27] When the data from the WHO and Jick et al. studies were reanalyzed using only cases and controls that were within 1 and 2 years, respectively, of each other's age, the increased risk of venous thromboembolism in users of third-generation, compared with second-generation, oral contraceptives persisted (OR 2.3; 95% CI 1.0, 5.5; and 2.2; 95% CI 1.3, 3.6, respectively).[26,27] Therefore, the use of 5-year age bands does not entirely explain the association.

Critics also contend that the studies are affected by several biases. Because of preferential prescribing, there was a higher percentage of first-time users among those taking third-generation, compared with second-generation, oral contraceptives.[28,29] Women who first begin taking oral contraceptives have a significantly higher occurrence of venous thromboembolism than long-term users. Part of this increased incidence of venous thrombosis may be due to a higher prevalence of undiagnosed factor V Leiden mutation among first-time, compared with long-term, users. The factor V Leiden mutation is an inherited defect that renders factor Va relatively resistant to inactivation by activated protein C (APC), which is a crucial step in the down-regulation of thrombin formation.[30] Women who are heterozygous for the factor V Leiden mutation have a 30- to 50-fold increased risk of venous thromboembolism when they take oral contraceptives.[19,31] Carriers of this mutation would be less likely to be found among long-term users because they would be more likely to have already had venous thromboembolism and discontinued their oral contraceptive. Because first-time use is associated with increased risk of venous thromboembolism, having more first-time users begin third-generation, rather than second-generation, oral contraceptives could create an apparent association between venous thrombosis and third-generation oral contraceptives, when the association is actually explained by increased numbers of women with factor V Leiden among first-time users.

When Lidegaard et al. controlled for duration of use, there was no longer a significant difference in risk of venous thrombosis between second- and third-generation oral contraceptive users (OR 1.44; 95% CI 0.83, 2.50).[20] In contrast, when Helmerhorst et al. recalculated their results after excluding first-time users, the increased risk of venous thromboembolism in third-generation, compared with second-generation, oral contraceptive users persisted.[32] Similarly, when only new users from the WHO study were analyzed, third-generation oral contraceptive users still had an increased risk of venous thrombosis, although the odds ratio was no longer significant (OR 2.4; 95% CI 0.5, 11.3).[33] In balance, differences in duration of use between second- and third-generation users may account for some, but not all, of the increased risk.

Another concern about these studies is whether women at higher risk of venous thromboembolism were preferentially prescribed third-generation oral contraceptives. In a study from Denmark, women with a familial disposition to thrombosis were four times more likely to be prescribed third-generation, rather than second-generation oral contraceptives.[28] This could lead not only to a false association between third-generation oral contraceptives and venous thromboembolism, but also to more testing for thromboembolic disease among third-generation oral contraceptive users. Such increased surveillance could result in an overestimation of the association between oral contraceptives and venous thrombosis. However, the most recent case-control study by Bloemenkamp et al. eliminated surveillance bias by matching cases to controls that were referred to the same diagnostic center for venous thrombosis testing.[21] In this study, the odds ratio for third-generation oral contraceptive use was similar to previous estimates, suggesting that surveillance bias did not significantly affect previous studies.[21]

Part of the reason for the controversy surrounding the studies was the lack of a biological explanation for why third-generation oral contraceptives might be associated with a higher risk of venous thromboembolism. Because it was believed that estrogen, not progesterone, was associated with venous thromboembolism, bias seemed a more logical explanation. However, a recent study explains biochemically how the type of progestin may affect thrombotic risk. Rosing et al. from the Netherlands found that third-generation oral contraceptives induced APC resistance similar in magnitude to the factor V Leiden mutation.[34] Second-generation oral contraceptives caused only partial APC resistance. Women without the factor V Leiden mutation who used third-generation oral contraceptives had a risk of venous thromboembolism that was similar to nonusers who were heterozygous for the mutation (6- to 9-fold). Third-generation oral contraceptive users who were heterozygous for the mutation had a 50-fold increased risk of venous thromboembolism, which was similar to that of homozygotes.[34] Thus, this study offers a possible biological explanation for association of third-generation oral contraceptives with venous thrombosis. However, it is unclear whether this mechanism played a substantial role in the increased risk of venous thromboembolism in the clinical studies.

## CARDIOVASCULAR RISK FACTORS

Because of their higher androgenicity, older oral contraceptives result in decreased high-density lipoprotein (HDL), increased low-density lipoprotein (LDL), and abnormal glucose tolerance tests.[35] The androgen activity of the older oral contraceptives also inhibits the estrogen-related increase in sex hormone binding globulin (SHBG), and low SHBG has been associated with an increased incidence of hypertension, diabetes, and cardiovascular mortality.[36] In contrast, because of their low androgenic activity, third-generation oral contraceptives actually increase HDL and decrease LDL. On average, desogestrel-containing oral contraceptives are associated with a 12.9% increase in HDL and a 2.1% decrease in LDL, while those with norgestimate result in a 9.9% increase in HDL and a 0.2% decrease in LDL.[15] Both desogestrel- and norgestimate-containing oral contraceptives are associated with increased triglycerides (29.3% and 14.8%, respectively).[15] Second-generation oral contraceptives increase triglycerides by 11% to 80%.[37–41] Third-generation oral contraceptives do not cause significant abnormalities in the glucose tolerance test and do not inhibit the estrogen-related increase in SHBG.[6,8,10,15,42,43]

## MYOCARDIAL INFARCTION

Multiple case-control and cohort studies from the 1960s and 1970s found an increased risk of myocardial infarction in users of oral contraceptives.[44–51] However, prescribing practices have changed since that time toward preferential use of low-dose oral contraceptives in younger women without cardiovascular risk factors. Although more recent, small case-control studies from the United States and United Kingdom have not shown a significant association between myocardial infarction and oral contraceptives,[52–55] the large multinational WHO study found that users of the low-dose oral contraceptives had an increased risk of myocardial infarction.[56] In the WHO study, the attributable risk of all oral contraceptives to myocardial infarction ranged from 2.73 per 100,000 nonsmokers under 35 years of age to 396.2 per 100,000 smokers aged 35 years or older.[56]

It was hoped that because third-generation oral contraceptives possess decreased androgen activity, they would be associated with a reduced risk of myocardial infarction. Although the number of events was relatively small ($n$ = 182), the Transnational study group did find that while second-generation oral contraceptive users had an increased risk of myocardial infarction (OR 3.21; 95% CI 1.65, 6.21), third-generation oral contraceptive users had no increased risk compared with nonusers (OR 0.79; 95% CI 0.30, 2.11)[2] (Table 4). In other words, third-generation users had about one third the risk of myocardial infarction as users of second-generation oral contraceptives (OR 0.27; 95% CI 0.09, 0.83).[2] The group at highest risk was smokers.[2]

A cohort study by Jick et al. found that risk of cardiovascular death in users of oral contraceptives containing the third-generation progestin desogestrel was about one half that of users of the second-generation progesterone levonorgestrel, although the difference was not statistically significant and there were only 15 cases.[22] A later case-control study by the same authors was also inconclusive.[57] The WHO study did not have sufficient power to examine whether progesterone dose or type had any effect on myocardial infarction risk.[56]

## STROKE

Although the first-generation oral contraceptives of the 1960s and 1970s were associated with both ischemic and hemorrhagic stroke, recent studies suggest that second-generation oral contraceptives with their lower dose of estrogen are associated with little or no increased risk of stroke in young women who do not smoke, have no

**Table 4. Studies of the Relative Risk of Cardiovascular Events in Users of Third-Generation Compared with Second-Generation Oral Contraceptives***

| Article | Year | Type of Study | Study/ CV Events, *n* | CV Event Studied | Adjusted OR (95% CI) for Second-Generation OCP Users Versus Nonusers | Adjusted OR (95% CI) for Third-Generation OCP Users Versus Nonusers | Adjusted OR (95% CI) for Third-Generation Versus Second-Generation OCP Users |
|---|---|---|---|---|---|---|---|
| Transnational study[2] | 1997 | Case-control | 817/182 | MI | 3.21 (1.65, 6.21) | 0.79, (0.30, 2.11)† | 0.27 (0.09, 0.83)‡§ |
| Jick et al.[22] | 1995 | Cohort | 303, 470/15 | Idiopathic CV death | | | Desogestrel: 0.4 (0.1, 2.1)<br>Gestodone: 1.4 (0.5, 4.5) |
| Jick et al.[57] | 1996 | Case-control | 55/11 | MI | | | Desogestrel: 0.7 (0.1, 8.2)<br>Gestodone: 0.6 (0.1, 6.4) |
| WHO Study Group[56] | 1997 | Case-control | 1,309/368 | MI | Europe: 5.01(2.54, 9.90)<br>Developing countries: 4.78 (2.52, 9.07) | Unable to determine | Unable to determine |

*CV indicates cardiovascular; OR, odds ratio; CI, confidence interval; OCP, oral contraceptive; MI, myocardial infarction.

†When norgestimate is considered a second-generation progestin, the OR does not change significantly (OR 0.82; 95% CI 0.29, 2.31).[2]

‡When norgestimate is considered a second-generation progestin, the OR does not change significantly (OR 0.28; 95% CI 0.09, 0.86).[2]

§When third-generation oral contraceptives are compared with levonorgestrel only, the OR does not change significantly (OR 0.27; 95% CI 0.09, 0.83).[2]

cardiovascular risk factors, and are screened for hypertension.[3,4] However, there may still be an increased risk of stroke in smokers and in those with high blood pressure, even among those using second-generation oral contraceptives with low doses of estrogen.[3,58–61]

Whether third-generation oral contraceptives are associated with a smaller risk of stroke compared with second-generation oral contraceptives has not been well studied. The WHO study found a difference in risk of ischemic stroke between users of third-generation and users of second-generation oral contraceptives in developing countries. This increased risk did not occur in European women, who were analyzed separately from those in developing countries because of differences in the prevalence of cardiovascular risk factors and oral contraceptive prescribing practices. In developing countries, second-generation oral contraceptive users had an increased risk of ischemic stroke (OR 3.38; 95% CI 2.23, 5.13), while third-generation oral contraceptive users had no increased risk (OR 1.18; 95% CI 0.24, 5.86)[58] (Table 5). In contrast, the Transnational study found stroke risk elevated similarly in users of second-generation (OR 2.6; 95% CI 1.7, 3.9) and users of third-generation oral contraceptives (OR 3.1; 95% CI 1.9, 5.0).[59] The WHO study did not find any difference between users of third-generation and users of second-generation oral contraceptives in terms of hemorrhagic stroke.[60] Unfortunately, two recent U.S. case-control studies by Petiti et al. and Schwartz et al. did not include women using the third-generation progestins.[3,4] However, they did compare two types of second-generation progestins, norgestrel (including levonorgestrel) and norethindrone, which has lower androgenicity. Schwartz et al. found that users of the norgestrel type of contraceptive had a higher risk of hemorrhagic stroke than norethindrone users (OR 3.23; 95% CI 1.24, 8.41),[4] suggesting that the type of progestin may play a role in stroke risk.

## DISCUSSION

Although the aggregate data suggest that third-generation oral contraceptives may be associated with increased venous thromboembolism compared with second-generation oral contraceptives, many experts still believe that bias is a plausible explanation for this. However, bias cannot explain the finding by Rosing et al. that third-generation oral contraceptives induce APC resistance of a similar magnitude as the factor V Leiden mutation (6- to 9-fold). Therefore, it is plausible that third-generation oral contraceptives do increase the risk of venous thromboembolism more than second-generation oral contraceptives.

However, preliminary studies, which contain relatively small numbers of cases, show that third-generation oral contraceptives also may be associated with a decreased risk of myocardial infarction. Although limited data indicate that third-generation oral contraceptives may not decrease stroke risk in young healthy women, they may prove to be useful for high-risk women.

Therefore, although users of third-generation oral contraceptives may have more overall adverse events because of an increased incidence of venous thromboembolism, this higher event rate does not necessarily translate into increased mortality. Indeed, while the case fatality rate of venous thromboembolism is estimated to be between 1% and 2%, the mortality rate of myocardial infarction in young women is estimated to be 50%.[62] Schwing and Shelton conducted a risk/benefit modeling analysis of incidence and mortality rates for venous thromboembolism and myocardial infarction according to type of oral contraceptive.[63] To estimate event rates in users, baseline risks of venous thromboembolism and myocardial infarction in nonusers were multiplied by estimated relative risks for each generation of oral contraceptive. Using the estimate that third-generation oral contraceptive users

**Table 5. Studies of the Relative Risk of Ischemic and Hemorrhagic Stroke in Users of Third-Generation Compared with Second-Generation Oral Contraceptives***

| Article | Year | Type of Study | Study/Strokes, *n* | Adjusted OR (95% CI) for Second-Generation OCP Users Versus Nonusers | Adusted OR (95% CI) for Third-Generation OCP Users Versus Nonusers | Adjusted OR (95% CI) for Third-Generation Versus Second-Generation OCP Users |
|---|---|---|---|---|---|---|
| Ischemic | | | | | | |
| WHO Study Group[58] | 1996 | Case-control | 2,659/697 | Europe: 1.53 (0.69, 3.39)<br>Developing Countries: 3.38 (2.23, 5.13) | Europe: 1.76 (0.33, 9.36)<br>Developing Countries: 1.18 (0.24, 5.86) | |
| Transnational Study[59] | 1997 | Case-control | 995/220 | 2.6 (1.7, 3.9) | 3.1 (1.9, 5.0) | 1.2 (0.7, 2.0) |
| Petiti et al.[3] | 1996 | Case-control | 520/142 | 1.18 (0.54, 2.84) | | |
| Schwartz et al.[4] | 1997 | Case-control | 55/6 | 0.90 (0.27, 2.94) | | |
| Hemorrhagic | | | | | | |
| WHO Study Group[60] | 1996 | Case-control | 3,978/1,068 | | | No difference, no data given |
| Petiti et al.[3] | 1996 | Case-control | 544/148 | 1.14 (0.60, 2.16) | | |
| Schwartz et al.[4] | 1997 | Case-control | 56/14 | 0.93 (0.37, 2.31) | | |

**OR indicates odds ratio; CI, confidence interval; OCP, oral contraceptive.*

are 0.36 times as likely to suffer a myocardial infarction, 0.6 times as likely to die from a myocardial infarction, and 2.0 times as likely to have or die from venous thromboembolism as second-generation oral contraceptive users, they found that women aged 15 to 34 years would have a similar overall mortality whether they used second- or third-generation oral contraceptives.[63] However, users of third-generation oral contraceptives who are aged 35 to 44 years would have a lower rate of death compared with users of second-generation oral contraceptives (3.4 vs 4.9 per 100,000), because of a lower rate of death from myocardial infarction.[63] In addition, third-generation oral contraceptives, because they are associated with fewer side effects and a higher continuation rate, may lead to a decreased rate of pregnancy compared with second-generation oral contraceptives. This could translate into a lower rate of venous thromboembolism and lower mortality rate because pregnancy is associated with a significantly higher rate of both mortality and venous thrombosis than any of the oral contraceptives.

Despite their association with venous thromboembolism, third-generation oral contraceptives' improved side-effect profile and possible decreased association with cardiovascular events make them a useful new class of oral contraceptives for most women. However, because of their possible induction of APC resistance, third-generation oral contraceptives should not be prescribed for women with a familial disposition to or risk factors for venous thromboembolism. Also, it is even more important that a physician follow the recommendation to discontinue oral contraceptives before prolonged immobilization or surgery that would predispose a patient to the development of venous thromboembolism when she is taking third-generation oral contraceptives. According to the modeled estimate by Schwing and Shelton, clinicians should especially consider prescribing third-generation oral contraceptives for older women, such as those aged 35 to 44 years. However, given the lack of rigorous studies of third-generation oral contraceptives in older women who smoke or have hypertension or hyperlipidemia and the likely increased risk, such women should still not be prescribed any type of oral contraceptive. Finally, third-generation oral contraceptives are an especially attractive option for women who cannot tolerate other methods of contraception. It is important to note that for these women, risk of venous thromboembolism is lower with third-generation oral contraceptives than with pregnancy.

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